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Genetic Heterogeneity in Catatonic Schizophrenia: A Family Study

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In a family study concentrating on 139 probands with chronic DSM-III-R schizophrenia, catatonic type, 83 probands (41 women, 42 men) met the criteria for periodic catatonia and 56 probands (14 women, 42 men) for systematic catatonia according to the Leonhard classification. The reliability and stability of this subclassification were tested by 2 experienced psychiatrists working independently of each other. Both diagnosticians were kept blind as to the probands' family history. The 139 probands had a total of 543 first-degree relatives. Only those hospitalized for schizophrenia were allocated to the group of afflicted family members. Diagnostic reliability was kappa statistic 0.93 and diagnostic stability during catamnesis reached 97% and kappa of 0.93. Life-table analysis revealed that the age-corrected risks were significantly different in periodic and systematic catatonia. In systematic catatonia mothers had a risk of 6.8%, fathers 2%, and randomly selected sibs 3%. In periodic catatonia an excess of homologous psychoses was apparent: There was a risk of 33.7% for mothers, 15.4% for fathers, and 24.4% for sibs. The quota of afflicted parents (33 of 161) was higher than that of sibs (26 of 162). In periodic catatonia, 59% of the families were multiple afflicted with pronounced unilineal vertical transmission. In 10% of the families 3 successive generations suffered from the disease and were treated in hospital. The results of the study led to the following hypotheses: Periodic and systematic catatonia are valid subgroups of DSM-III-R schizophrenia. In systematic catatonia heritability is very low. Periodic catatonia is a familial disorder. Homogeneity of familial psychoses and unilineal vertical transmission with anticipation are consistent with a major gene effect. Periodic catatonia seems to be a promising candidate for molecular genetic evaluation. © 1996 Wiley-Liss, Inc.

KEY WORDS: psychosis, catatonia, genetics, major gene effect, Leonhard classification

INTRODUCTION

It remains controversial whether in psychiatric research there is clinical evidence for distinct nosological entities and whether familial aggregation of the disorders provides insights into etiology [Dalen and Hays, 1990; Andreasen and Carpenter, 1993; Cloninger, 1994; McGuffin et al., 1994; Pichot, 1994]. In schizophrenia, family studies are a powerful tool for estimating the degree of familial aggregation and the influence of genetics [McGue and Gottesman, 1989; Tsuang et al., 1991].

FAMILIAL AGGREGATION OF SCHIZOPHRENIA

Based on the Kraepelinian concept of chronically dissociative and avolitional processes in schizophrenia ("dementia praecox"), early European studies found a risk of 6.6–8.1% morbidity in first-degree relatives of schizophrenics [Slater and Cowie, 1971; Gottesman and Shields, 1982]. Overestimating Schneiderian first-rank symptoms and making an extraordinarily narrow definition of schizophrenia, psychiatric epidemiologists found no evidence of familial transmission [Abrams and Taylor, 1983; Pope et al., 1982]. To overcome methodological criticism [Weissman et al., 1986], most recent family studies have used structured psychiatric assessment, operational diagnostic criteria, blind assessment, and blind diagnosis. Familial aggregation of schizophrenia was not convincing in small sample sizes [Coryell and Zimmerman, 1988; Gershon et al., 1989], but others found that the risk to relatives was about 10 times that of controls [Baron et al., 1985; Frangos et al., 1985; Kendler et al., 1985, 1993; Maier et al., 1993]. Recent studies by Kendler et al. [1993] and Maier et al. [1993] of 126 and 146 families, respectively, reported a cumulative risk in first-degree relatives of 6.5% and 5.2%. These results confirmed that there was no signif-

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icant variation between samples and that narrowly defined schizophrenia [American Psychiatric Association, 1987] is a familial disorder.

SCHIZOPHRENIA IN PARENTS AND SIBS OF SCHIZOPHRENIC PATIENTS

Family studies agree that the risk for parents is much lower than that for sibs. Summarizing earlier literature, Zerbin-Rüdin [1967] cited a rate of 8.6% (±3.4 SD) in sibs and 4.4% (±0.2 SD) in parents. In family studies since 1980, the morbidity risk in schizophrenics' first-degree relatives varied from 8.3 to 9.2% in sibs and from 1.1 to 5.8% in parents [Alda et al., 1989; Baron et al., 1985; Kendler et al., 1993; Maier et al., 1993]. Another indubitable finding is that, among afflicted parents of schizophrenic patients, mothers clearly outnumber fathers. Earlier studies of 1,777 schizophrenic patients [Essen-Møller, 1963] found 3.5% (±0.4 SD) of mothers schizophrenic compared to 1.6% (±0.3 SD) of fathers. Similar findings have been reported more recently [Bleuler, 1978; Shimizu et al., 1987]. Homogeneity of familial morbidity was often observed by investigators [Scharfetter and Nüsperli, 1980; Gottesman and Shields, 1982], but was questioned by those using gross diagnostic categories or factor analysis of symptoms [Kendler et al., 1988; Leboyer et al., 1992]. Their results seem consistent with a familial continuum from schizophrenia to affective psychosis and spectrum disorders [Crow, 1986; Maier et al., 1993]. Thus, taking schizophrenia as one disease entity, multifactorial polygenic models of transmission seem to be the most appropriate [Kidd, 1981; Tsuang et al., 1991]. However, it remains unresolved just why schizophrenia is more familial in some pedigrees with traits of partly dominant inheritance [Karlsson, 1992] than in others.

HETEROGENEITY OF FAMILIAL AGGREGATION IN SCHIZOPHRENIC SUBTYPES

Another approach is to divide the disease into clinically different subtypes. Kraepelin [1919, 1971] had strongly recommended using subtypes of chronic psychoses ("dementia praecox") and sought to differentiate between hebephrenic, catatonic, and paranoid syndromes. In catatonia, Kallmann [1938] found a high familial incidence of homogeneous psychoses amounting to 18.8% in parent-child pairs and a significantly increased morbidity risk of 9.6% in sibs. These findings were confirmed by Weinberg and Lobstein [1943] and Hallgren and Sjøgren [1959]. They reported that patients with predominantly catatonic symptoms had an increased familial incidence (8.3% and 8.5%) compared to paranoid schizophrenic patients (3.1% and 4.7%, respectively). Scharfetter and Nüsperli's family study [1980] also showed a significantly increased morbidity risk in first-degree relatives of catatonic patients (12.8%) compared to patients with paranoid (6.5%) and hebephrenic-type schizophrenia (8.4%). Furthermore, in catatonia the morbidity risk for homotypical psychoses in relatives was the most prominent compared to other functional psychoses.

DIAGNOSTIC ASSESSMENT OF CATATONIA IN MODERN PSYCHIATRY

Although catatonia is incorporated in psychiatric classifications as a subtype of schizophrenia [APA, 1987; World Health Organization, 1991], it is largely neglected by clinicians [Mahendra, 1981; Kendler et al., 1988; Rosebush et al., 1990; Fink and Taylor, 1991]. This is mainly due to changes in the concepts of schizophrenia and by how much the paranoid-hallucinatory syndrome has been accentuated in recent operationalized diagnostic procedures. According to DSM-III-R the catatonic-type schizophrenia is sufficiently described if marked nondirectional hyperkinesis or akinesis is predominate in the clinical picture [APA, 1987]. Rating scales reducing psychomotoric disturbances to "one-way" hyperactivity or underactivity in spontaneous involuntary movements failed, however, to define catatonia as a valid schizophrenic subtype [Manschreck, 1986; McKenna et al., 1991; Caligliuri et al., 1993]. Furthermore, psychomotoric symptoms such as stupor, mutism, negativism, rigidity, excitement, or posturing have also been viewed as manifestations of organic cerebral diseases or as preceding states of neuroleptic malignant syndrome [White and Robins, 1991; Johnson, 1993; Carroll et al., 1994].

THE WERNICKE-KLEIST-LEONHARD SCHOOL AND DIFFERENTIAL PSYCHOPATHOLOGY OF CATATONIA

The Wernicke-Kleist-Leonhard school postulated various distinct endogenous psychoses with different patterns of heredity [Leonhard, 1979, 1995; Hamilton, 1984; Ungvari, 1993]. As a result of thorough follow-up investigations, Leonhard classified endogenous psychoses into 5 main categories according to different symptomatology, long-term course, and outcome:

1. Unipolar phasic psychoses
2. Bipolar phasic psychoses
3. Cycloid psychoses
4. Unsystematic schizophrenias
5. Systematic schizophrenias

This highly operationalized classification system is of outstanding reliability and validity [Fish, 1957, 1964; Astrup, 1979; Wilson and Ban, 1983; Ungvari, 1985; Ban, 1990; Franzek and Beckmann, 1992a,b; Beckmann et al., 1992]. Leonhard's unipolar-bipolar concept of affective disorders has already been incorporated in modern classification systems. Many investigators have scrutinized the prognostic validity of cycloid psychosis [Perris, 1974; Cutting et al., 1978; Brockington et al., 1982; Maj, 1990; Beckmann et al., 1990; Jonsson et al., 1991] and it has been included as a separate category in ICD 10 [WHO, 1991]. Long-term clinical follow-up studies confirmed the reliability of the unsystematic-systematic dichotomy in chronic schizophrenia [Fish, 1957; Astrup, 1979; Franzek and Beckmann, 1992a]. This dichotomy was further corroborated in clinicogenetic studies [Astrup, 1979; Ungvari, 1985], and in those on corresponding prevalence rates in different

populations [Wilson and Ban, 1983] and in those reporting different responses to pharmacological treatment [Fish, 1964; Ban, 1990; Beckmann et al., 1992].

Complex psychomotoric distortion of involuntary movements and behavior in chronic catatonic-type schizophrenia was meticulously described by Kleist [1960], Gjessing [1976], and Leonhard [1979]. Catatonic-type schizophrenias were dichotomized into periodic and systematic catatonia based on different symptomatology, course, and residual states. Periodic catatonia belongs to the main category of unsystematic schizophrenia types, typically runs an intermittent course, and exhibits bipolar psychomotoric disturbances leading to adynamic residual states. The characteristics comprise simultaneous quantitative (hyperkinetic or akinetic) and qualitative (parakinetic) distortion of psychomotoric activity. Symptom patterns tend to be polymorphous during acute attacks. In contrast, symptomatology and the clinical pictures of systematic catatonia types are clear-cut and unequivocal. During the first years these diseases, which usually begin insidiously, often have nonspecific "accessory" symptoms, such as mood swings, hallucinations, or delusions, but even at the onset the characteristic syndromes, which remain unchanged in the long run, can be observed. Leonhard reported significantly different heredity in periodic and systematic catatonia. In systematic catatonia a positive family history was rare (3–4%), whereas periodic catatonia had a high familial incidence with homogeneous psychoses (about 20%).

AIMS OF THE STUDY

The study was designed to test 1) Leonhard's postulate of clinical dichotomy for chronic catatonic schizophrenia into periodic and systematic catatonia regarding their different cross-sectional pictures and type of long-term course, and 2) whether the 2 clinical entities emanate from different genetic backgrounds. We calculated the morbidity risk separately for mothers, fathers, and sibs using a conservative approach to life-table analysis. We tested 3) the hypothesis as to whether the morbidity risk is similar among parents, and we examined 4) the occurrence of homotypical familial aggregation and discussed to what degree "schizophrenia" is a familial disorder when considered a disease entity.

SUBJECTS AND METHODS

Selection of Probands

Probands were chosen from inpatients and outpatients at the Department of Psychiatry, Wuerzburg University, and from wards with chronically ill patients and rehabilitation units at the Lohr/Main State Hospital. Seven hundred forty-nine patients were recruited between April 1991 and October 1992. Public psychiatric care is such that patients with chronic diseases are predominantly admitted to one of the two hospitals. Both hospitals serve the city of Wuerzburg (130,000 inhabitants) and the surrounding mostly rural area.

Diagnostic Categories

Patients had to fulfill diagnostic criteria for schizophrenia according to DSM-III-R [APA, 1987]. As the Leonhard's classification may be largely unknown in Anglo-American literature, some basic information on psychopathology and the course of periodic and systematic catatonia which this study refers to, is provided [Leonhard, 1979, 1995].

Periodic catatonia. Periodic catatonia is one subtype of Leonhard's main category of unsystematic schizophrenia. The course is typically intermittent and bipolar with both hyperkinetic and akinetic states. During acute attacks, symptoms of the hyperkinetic and akinetic poles are characteristically intermingled. Thus, with akinetic traits, hyperkinesis displays peculiar rigidity. Natural grace gives way to jerky clumsiness and movements are stiff, generally becoming repetitive and monotonous, either as a stereotype or iteratively. The distortion of psychomotoric activity leads to grimaces, parakinetic movements, impulsive actions with aggressiveness, and negativistic behavior. Expressive motions are without meaningful content. Depressive, expansive or irritable mood swings, delusions, and hallucinations occur without being prominent and usually disappear during remission. After one or more attacks, residual states of varying degrees develop, ranging from mild defects with poverty of movement, blunted affect, and lack of motivation to very severe cases with marked obtuseness and numbness. Even in severe residual states, symptoms of both poles, hyperkinesia and akinesia, are present simultaneously. Single movements and gestures are inharmonious, stiff and distorted, and grimaces occur particularly in the upper part of the face. Impulsive actions and sometimes linguistic impulsiveness are characteristic.

Systematic catatonia. Systematic catatonia types usually begin insidiously and run a chronically progressive course without remission. Their irreversible, treatment-resistant residual states are distinctly characterized and can be reliably distinguished from periodic catatonia [Leonhard, 1979; Ban, 1982; Ungvari and Rankin, 1990; Franzek and Beckmann, 1992a].

Final Diagnostic Assessment

As an initial step, G.S. screened the hospital records of 749 schizophrenic patients for a display of catatonic symptoms cross-sectionally and/or in the long run according to DSM-III-R. In 183 patients (24.4%), catatonic features were documented at least once during their illness. These patients were examined by 2 experienced psychiatrists (E.F., H.B.), working independently of each other and diagnosing according to Leonhard's nosology. Psychopathology in the case notes at their disposal was documented according to the views of diagnostic systems used at that time (ICD 9, [WHO, 1978]). They contained no information about familial affliction, so the diagnosticians were blind to the probands' family history.

Forty-four of the 183 patients (24%) did not meet the diagnostic criteria of either systematic or periodic catatonia. One hundred thirty-nine patients presented unequivocal syndromes of periodic and systematic catatonia.

Diagnostic reliability was tested in a subsample of 32 of the 183 patients selected by G.S. Both psychiatrists (E.F., H.B.) independently diagnosed them using

the highly sophisticated and operationalized descriptions of Leonhard [1979]. The coefficient of concordance of the two investigators was reached according to Cohen [1960]. To test diagnostic stability, the 139 patients meeting the criteria for periodic or systematic catatonia had follow-up examinations by the two clinicians. The examinations ranged between 6 months and 2 years apart. Kappa statistics were also used to compare diagnostic stability.

The final diagnostic group of 139 probands consisted of 83 patients (41 women, 42 men) with periodic catatonia and 56 patients (14 women, 42 men) with systematic catatonia. At least once during the course of their illness, all the probands met the diagnostic criteria of schizophrenia, catatonic type, according to DSM-III-R.

The mean age (±standard deviation) of periodic catatonic patients was 46.5 years (±16.8) at the time of assessment (Table I). The mean duration of the disease was 22.7 years (±15.0) and the mean age at initial hospitalization was 24.8 years (±9.6). Men were insignificantly younger at initial hospitalization (23.2 years ± 8.0 SD) than women (26.5 years ± 10.8 SD). The mean age of the 56 patients with systematic catatonia (Table I) was 40.7 years (±14.1), the mean duration of the disease being 21.0 years (±13.7) and the mean age at initial hospitalization 20.8 years (±7.0). In these cases, there was no difference in age at initial hospitalization between men (20.8 years ± 6.9 SD) and women (20.7 years ± 7.8 SD).

Multiple Ascertainment

In this study each proband represented one pedigree. No proband appears as an affected relative. This approach avoided multiple ascertainment. Thus, we excluded one major bias which could have exaggerated the morbidity risk in one diagnostic group with increased familial affliction.

Evaluation of the Morbidity Risk in First-Degree Relatives

Family history data were collated from two different sources. We turned first to patients' hospital records with information from family doctors, reliable relatives, and acquaintances. For further information on their psychiatric family history, G.S. then contacted living first-degree relatives (mostly parents) of 45 of 56 (80%) families with systematically catatonic patients and 59 of 83 (71%) families of periodically catatonic patients. Extensive pedigree data were recorded on each patient's family. To avoid exaggerating the morbidity risk, particularly from subjective statements of patients and/or their relatives, we did not include the multiinformant family history in this report [Andreasen et al., 1986]. To obtain reliable data concerning the morbidity risk, age at initial hospitalization, and familial psychopathology, we allocated only those relatives with documented psychiatric hospitalization to the group of afflicted family members. A blind diagnostic review of these hospital records was made by 2 experienced clinicians using DSM III-R for schizophrenia.

Statistical Methods

In this report we have used the life-table analysis based on the Kaplan-Meier method to calculate the age-specific morbidity risk. The difference in life-table curves for different groups was determined by the log-rank χ^2 statistics with one degree of freedom. Unknown fathers were excluded from analysis. A difficult problem in family studies is that relatives do not constitute strictly independent data points. This remained unresolved in recent family studies on schizophrenia which took the individual relative as the unit of analysis [Kendler et al., 1993; Maier et al., 1993]. This study has adopted a more conservative approach and divides families into independent categories: mothers, fathers, and sibs. Calculating the age-corrected morbidity risk in parents separately presented no problems. Determining the morbidity risk among sibs was, however, difficult, since sibs are not a priori independent data points. We took a conservative approach, calculating the morbidity risk for a randomly selected sib in each family. We used this statistical standard in this first analysis of the age-specific life-time morbidity risk in periodic and systematic catatonia, even though there may be no substantial bias if remaining sibs are included.

As a second step, for parents and sibs of periodically catatonic patients, we calculated multivariate survival analysis using Cox's regression model censored for the gender of the proband and relative [Cox, 1972; Christensen, 1987]. This yielded risk curves with significant prognostic indices for parents and sibs by combining the two censored variables. The prognostic index can be translated into estimates of the probability of disease development within a given time for the subject

TABLE I. Demographic and Clinical Characteristics of Patients With Systematic and Periodic Catatonia (Mean Values ± Standard Deviation)*

	Systematic catatonia			Periodic catatonia		
	Female and male (n = 56)	Male (n = 42)	Female (n = 14)	Female and male (n = 83)	Male (n = 42)	Female (n = 41)
Patients' age at assessment	40.7 ± 14.1	41.1 ± 13.6	39.7 ± 16.1	46.5 ± 16.8	43.1 ± 14.7	50.0 ± 18.2
Age at initial admission	20.8 ± 7.0	20.8 ± 6.9	20.7 ± 7.8	24.8 ± 9.6	23.2 ± 8.0	26.5 ± 10.8
Duration of illness	21.0 ± 13.7	21.3 ± 13.9	20.0 ± 13.5	22.7 ± 14.0	20.9 ± 14.6	24.6 ± 15.3
Frequency of admissions	3.2 ± 3.3	3.0 ± 2.9	3.9 ± 4.3	6.2 ± 5.2	6.3 ± 4.9	6.1 ± 5.6

*Using t test no significant differences were obvious between males and females in both diagnostic groups.

concerned, i.e., the cumulative "survival" probability indicates the cumulative probability of a particular subject not being psychiatrically ill at a given time.

To analyze demographic variables, we used the unpaired, one-tailed Student's t test and the nonparametric Mann-Whitney U test. The χ^2 test was used to compare multiple-afflicted families in the two diagnostic systems. The coefficient of concordance by two psychiatrists, i.e., identical allocation to periodic or systematic catatonia, was reached according to Cohen [1960].

RESULTS

Diagnostic Reliability and Stability

In a subsample of 32 of 139 probands we tested the reliability of the two diagnosticians (E.F., H.B.). They disagreed on one patient (3%) who suffered from a combined systematically catatonic form (consensus diagnosis). The degree of agreement was 0.93 according to Cohen's kappa. During the catamnestic examinations (ranging from 0.5 to 2 years) we had to change the initial diagnosis in four of the 139 patients (3%). Diagnostic stability, i.e., identical diagnoses in both examinations, was 97% and the kappa statistic 0.93.

One male patient initially diagnosed with systematic catatonia (parakinetic form) was clearly periodic, with hyperkinetic and akinetic features developing into a severely adynamic, apathetic, residual state. Diagnosis was changed to periodic catatonia. One female patient experienced a period of extreme aggressive psychomotoric excitement on initial examination and so was diagnosed with periodic catatonia. She subsequently developed a typical syndrome of systematic catatonia (negativistic form) that had obviously been present for several years. Two patients initially appeared to have unspecified residuals and were diagnosed with a residual state of periodic catatonia. Further examination, however, revealed the psychopathology typical of combined systematically catatonic syndromes (parakinetic-negativistic forms). There was no misclassification between catatonic patients and other clinical subforms of schizophrenic psychoses according to Leonhard.

Assessment of First-Degree Relatives

We first analyzed the number of afflicted first-degree relatives in the sample of 139 periodically and systematically catatonic patients using definitive biographical data on all mothers and sibs including whether or not they were hospitalized. In periodic catatonia there were 5 (6.0%) and in systematic catatonia 3 (5.4%) unknown fathers. Thus, this family study on periodic and systematic catatonia as clinical subforms of DSM-III-R schizophrenia is based on the evaluation of 543 first-degree relatives.

Table II shows the number of mothers and fathers, and how many received psychiatric hospitalization for schizophrenia. All case notes on the 70 hospitalized first-degree relatives were available. In 64 cases two clinicians working independently diagnosed schizophrenia definitively by reviewing the case notes. Two further diagnoses of schizophrenia were diagnosed by consensus (for one relative of a periodically and one relative of a systematically catatonic patient). Case notes of four relatives of periodically catatonic patients revealed no definitive schizophrenic symptomatology, but:

1. A depressive syndrome accompanying treatment-resistant trigeminal neuralgia;
2. A depressive syndrome following a right-hemispheric stroke with hemiparesis;
3. A confused state in diabetogenic hypoglycemia;
4. Alcoholism.

Systematically catatonic patients (n = 56) had 220 first-degree relatives. Four of 109 parents and 3 of 111 sibs were afflicted with schizophrenia. Periodically catatonic patients (n = 83) had 323 first-degree relatives. Thirty-three of 161 parents and 26 of 162 sibs were afflicted with schizophrenia. Forty-two of the 59 afflicted relatives of periodically catatonic patients were alive. Hitherto, we had been able to examine 32 (76%) of them personally. All of them had residual states characteristic of periodic catatonia.

Procreative fertility in the parental lines of both subsamples of catatonic patients was the same. The mean number (±standard deviation) of sibs was 2.0 (±1.8) in systematic catatonia and 2.0 (±1.6) in periodic catatonia. Probands with periodic catatonia whose parents were afflicted had the same quota of sibs (2.0 ± 1.8) as those with parents clinically unafflicted (1.9 ± 1.4).

Familial Analysis

In systematic catatonia, the seven relatives afflicted were from six families. The proportion of multiple-afflicted families was 11%. In contrast to this, 49 of the 83 (59%) nuclear families of periodically catatonic patients were multiple afflicted. Forty families had one afflicted member, eight families had two, and one nuclear family had three. The proportion of families with one or more schizophrenic members differed significantly in both diagnostic groups ($\chi^2 = 32.7$; df = 1; $P < .001$).

Age-Specific Morbidity Risk Among Parents

Figure 1 illustrates the risk of schizophrenia in mothers using the life-table method based on the Kaplan-Meier estimates. Three of 56 mothers of systematic catatonic patients and 22 of 83 mothers of periodic catatonic patients were afflicted. Statistics show only a slight increase in the life-time morbidity risk for mothers of systematic catatonics. In periodic catatonia, how-

TABLE II. Numbers of Schizophrenic First-Degree Relatives in Patients With Systematic and Periodic Catatonia

	Systematic catatonia (n = 56)		Periodic catatonia (n = 83)	
	No.	Affected	No.	Affected
First-degree relatives				
Fathers	53	1	78	11
Mothers	56	3	83	22
Brothers	61	3	82	13
Sisters	50	0	80	13
Σ	220	7	323	59

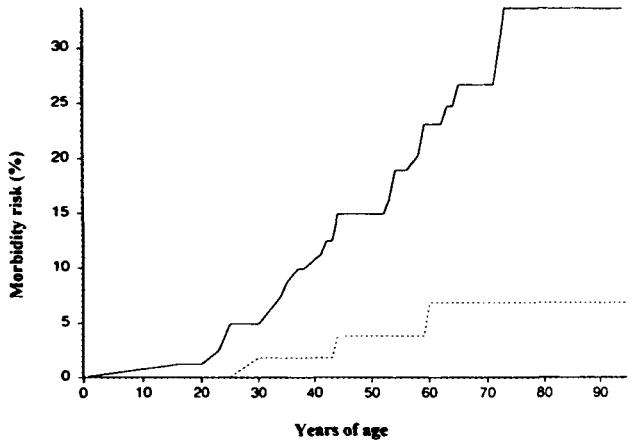

Fig. 1. Catatonic types of schizophrenia and the morbidity risk of schizophrenia for mothers: Comparison between mothers of systematically catatonic patients (dotted line) and periodically catatonic patients (straight line). The life-table curves show only a slight increase in the risk for mothers of systematically catatonic patients up to a level of 6.8%. In periodic catatonia, however, the age of onset extends from 16 to 75 years. The mothers' risk rises continuously, attaining a level of 33.7%. This difference between both diagnostic groups is statistically significant ($P < 0.005$, Kaplan-Meier analysis for life-table analysis with log-rank test).

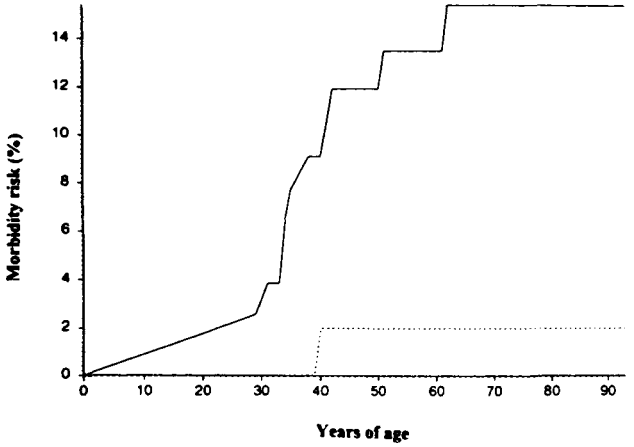

Fig. 2. The morbidity risk of schizophrenia for fathers of systematically catatonic (dashed line) and periodically catatonic patients (straight line): The life-time risk for fathers of systematically catatonic patients is 2.0%, that of periodic catatonic patients 15.4%. This is statistically significant at a level of $P < 0.02$ (life-table analysis based on the Kaplan-Meier method).

ever, the mothers' risk curve rises continuously until late in life. The age of onset extended from 16 to 75 years. Nearly one third of these mothers became clinically afflicted and needed treatment for schizophrenia at a psychiatric hospital. This marked difference is reflected by a risk of 6.8% for systematic catatonia and of 33.7% for periodic catatonia ($P < 0.005$) in mothers.

Figure 2 shows life-table graphs for fathers. While in systematically catatonic patients, one father was afflicted and the age-corrected morbidity risk was 2.0%, 11 fathers of periodically catatonic patients suffered from the disease and the age-specific morbidity risk was 15.4%. This difference between the 2 diagnostic groups was statistically significant ($P < 0.02$).

Age-Specific Morbidity Risk Among Sibs

To estimate the risk for sibs (Fig. 3), we selected one sib randomly from each family. Fourteen (17%) probands with periodic and 10 (18%) with systematic catatonia were an only child. Thus, in this evaluation, sibs were selected from 69 families with periodically and 46 families with systematically catatonic patients. The life-time morbidity risk for the latter was 3.0% and that for the former 24.4%. This difference was statistically significant ($P < .01$). In sibs of periodically catatonic patients, morbidity was 20.6% at the age of 35. At the time of assessment, 56% of the nonafflicted sibs were younger than 50 years and still at risk. Further late manifestations may occur in this group.

Comparison of the Morbidity Risk for Parents on the Basis of Life-Table Analysis

In systematic catatonia, the course of the life-time morbidity risk did not differ between fathers (2.0%) and mothers (6.8%). There was a substantial difference in periodic catatonia. Here, the morbidity risk of mothers was 33.7% and that of fathers only 15.4%. Figure 4, however, shows that the 2 curves are not nearly as different as supposed when only pure percentage rates were considered. Life-table analysis revealed no significant difference in the morbidity risk between fathers and mothers. Up to the age of 50 years both graphs run parallel and the risk for both sexes is about 15%. From then on, the morbidity risk continues to increase only for mothers.

Risk for Psychosis in Parents and Sibs of Periodically Catatonic Patients on the Basis of Multivariate Failure Curves

We calculated multivariate survival analysis in periodically catatonic patients censored by the gender of the proband and the relative. The estimated morbidity risk of 161 parents was $\beta = 0.617$ (± 0.368), i.e., the

Fig. 3. Differences in the life-time morbidity risk for sibs of systematically catatonic (dashed line) and periodically catatonic patients (straight line): The morbidity risk was calculated for one randomly selected sib from each informative family. In systematic catatonia the risk of schizophrenia is 3.0%, in periodic catatonia 24.4%. This is statistically significant at a level of $P < 0.01$ (life-table analysis based on the Kaplan-Meier method).

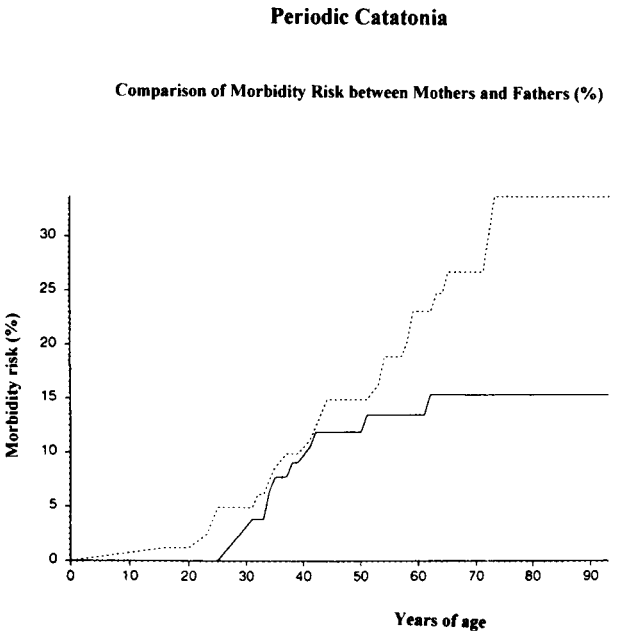

Fig. 4. The age-specific morbidity risk for parents of probands with periodic catatonia: Using life-table analysis the morbidity risk is clearly different, being 33.7% for mothers (dashed line) and 15.4% for fathers (straight line). Twenty-two mothers and 11 fathers of the 83 periodically catatonic patients were afflicted. However, the life-time risk in the parental lines shows no true differences by pairwise comparison with the log-rank test ($P < 0.1$). The risk runs parallel up to the age of 50. From then on only the risk for mothers continues to increase, whereas that of fathers levels out at 15%.

probands' gender made no significant difference to the morbidity risk of mothers and fathers ($P < 0.1$). The estimated morbidity risk of the 162 sibs was $\beta = -0.033$ (± 0.394), i.e., the adjusted prognostic variables had no significant impact on the morbidity risk ($P < 0.9$).

Patterns of Familial Aggregation in Nuclear Families and Extended Pedigrees

In systematic catatonia, seven of 220 first-degree relatives were afflicted. This resulted in a morbidity risk of 4.6% among first-degree relatives. Extended pedigrees demonstrate that in general these chronic-progressive forms of schizophrenia occur sporadically. In none of the 56 families with systematically catatonic patients did the disease extend through three successive generations.

Periodic catatonia showed a surplus of familial aggregation of homogenous psychoses and pronounced vertical transmission. In 83 families with 33 afflicted parents we were able to record 29 cases of unilineal transmission, and in two cases both parents were afflicted. In nine cases the disease was derived paternally and in 20 cases maternally. The rate of afflicted sibs (26 of 162) was lower than that of the parents (33 of 161). The age-corrected morbidity risk for first-degree relatives (parents and sibs) was at a level of 26.9%. In 8 of the 83 families (10%), 3 successive generations of family members had suffered from homogenous catatonic psychoses and received hospital treatment. Figure 5 depicts four of the eight pedigrees with three successive generations of periodic catatonia.

DISCUSSION

The aim of this study was to evaluate hypotheses dealing with the different genetic backgrounds in subgroups of 139 chronic DSM-III-R schizophrenic patients [APA, 1987] who had had symptoms of catatonia at least once. Statistically, the familial aggregation of schizophrenia was significantly different in subgroups when Leonhard's sophisticated differentiation between catatonic schizophrenic syndromes was applied [Leonhard, 1979, 1995]. Eighty-three patients (59.7%) suffered from periodic catatonia, with acute hyperkinetic or akinetic shifts, parakinetic distortion of movements resulting in residual states with poverty of movement, blunted affect, and impoverished drive and motivation. Fifty-six patients (40.3%) were diagnosed with systematic catatonia with chronic nonremitting course and clinically well-defined residual states that were irreversible, unchangeable, and completely resistant to neuroleptic treatment [Astrup, 1979; Beckmann et al., 1992]. The findings of the present study give intriguing evidence that systematic catatonia is, for the most part, a sporadic form of schizophrenia, whereas periodic catatonia aggregates in families in a manner consistent with a major gene effect.

Methodology, Diagnostic Reliability, and Stability

To differentiate clinically periodic catatonia from systematic catatonia according to the Leonhard classification, thorough (often manifold) examinations by experienced, well-trained psychiatrists are required. Diagnoses and subtype ascertainment were done independently and diagnosticians were blind to probands' family history. In a previous study with chronic schizophrenia Franzek and Beckmann [1992a,b] reached a concordance rate with Cohen's kappa of 0.87. In the present study Cohen's kappa was 0.93. During catamnestic examinations, initial diagnoses in 4 of 139 (3%) probands had to be changed from periodic to systematic catatonia or vice versa. No misdiagnosis had occurred with regard to hebephrenia or paraphrenia according to the Leonhard classification. Diagnostic stability was at a level of kappa 0.93. This unequivocally corroborates corresponding findings of preceding clinical investigations that periodic and systematic catatonia may present 2 different clinical entities [Leonhard, 1979; Fish, 1957; Astrup, 1979; von Trostorff and Leonhard, 1990; Franzek and Beckmann, 1992a]. In the whole catatonic group, sex ratio was 1.5, 84 males and 56 females, which corresponds to the literature [Scharfetter and Nüsperli, 1980]. Using Leonhard's classification, however, males outnumber females only in the systematic (sporadic) catatonic group, whereas the periodic (familial) catatonic group reveals equal sex distribution, giving a further hint to the genetic basis of this disease.

How to define the age of onset in mental diseases is a moot point [DeLisi, 1992]. Because all case notes of hospitalized probands and their sick relatives could be traced, we decided to define the age of onset as the patient's age on initial hospitalization. This approach is rather conservative, but these objective data are the most reliable for calculating age-corrected life-time morbidity risks. In addition, periodic catatonia usually

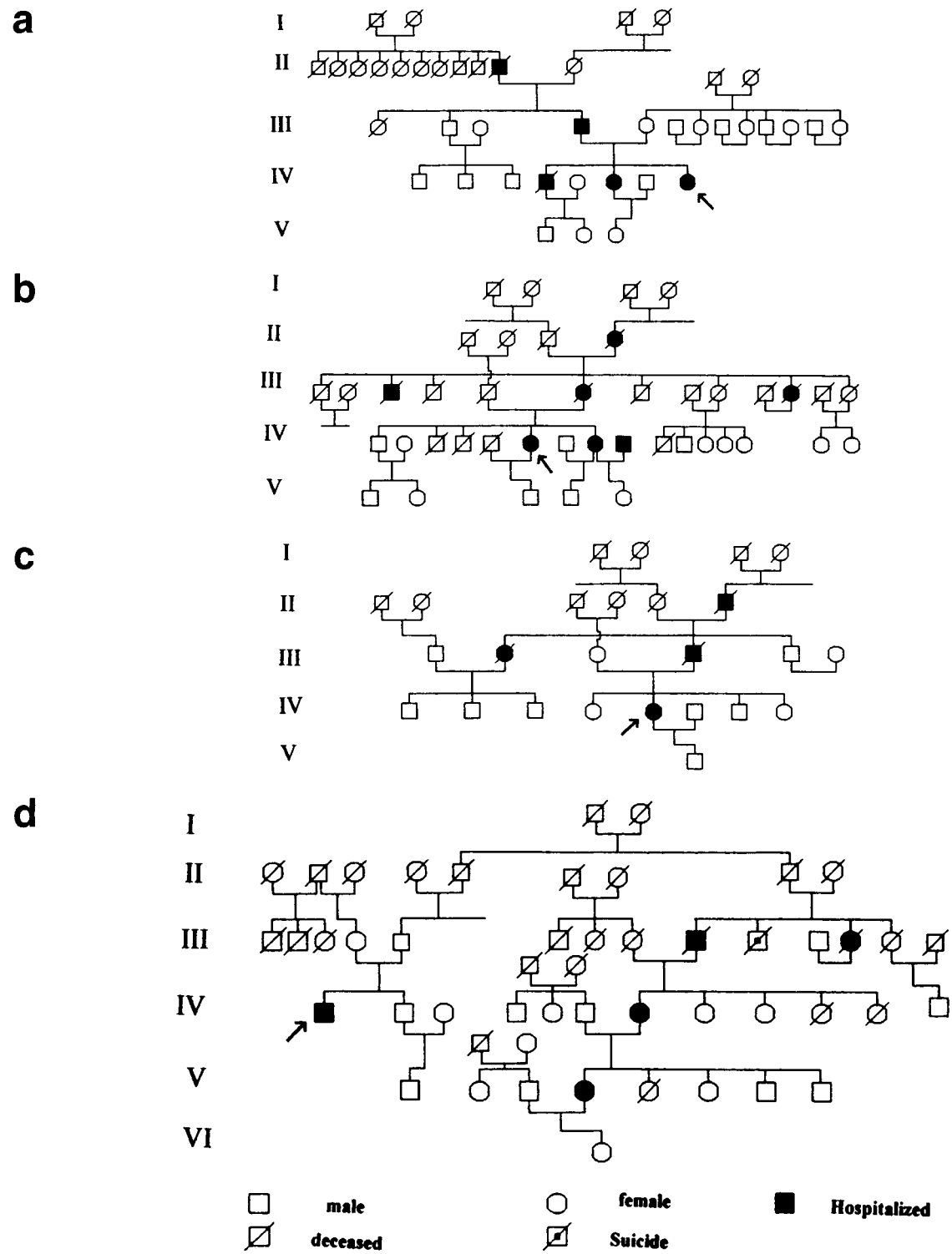

Fig. 5. **a–d:** Familial aggregation of periodic catatonia in extended pedigrees: Family pedigree from probands with periodic catatonia extending over 3 successive generations. Circles represent female patients, squares male patients, slashed symbols deceased individuals, target symbols suicides, solid symbols patients who received hospital treatment for periodic catatonia, and arrows the probands.

begins with acute and severe psychotic attacks that frequently cannot be handled in outpatient care and require hospitalization [Astrup, 1979; Franzek and Beckmann, 1992a]. Therefore, in most cases of periodic catatonia, the time of initial hospitalization [24.8 years ± 9.6 SD) coincided with the time of onset of the disease. In systematic catatonia the age of initial hospitalization was 20.8 years (±7.0). As systematic catatonia often begins imperceptibly and insidiously, the age of onset may actually be lower than estimated with this method. However, the age of onset of our probands was similar to that reported in most other family studies [Baron et al., 1985; Kendler et al., 1993; Maier et al., 1993]. This ruled out that age of onset had substantially biased proband selection.

To obtain a sufficient sampling of chronically catatonic schizophrenic patients, we had to use the "sample of convenience" strategy and recruit probands admitted to a psychiatric hospital [Ritsner et al., 1991]. Compared to an epidemiological approach this may lead to an overrepresentation of multiple-afflicted pedigrees. However, this would affect both diagnostic groups. It would have led to an increased morbidity risk in general and would not have been confined to periodic catatonia. Furthermore, this effect was referred to "schizophrenia of early onset," implying that more severe cases consequently have heavier genetic loading [Ritsner et al., 1991]. In our sample earlier onset was prominent in systematic catatonia with familial loading only rarely occurring afterwards.

Incidence of Schizophrenic Psychoses in Families With Chronic DSM-III-R Schizophrenia, Catatonic Type

Among 543 first-degree relatives of 139 chronic DSM-III-R schizophrenic probands who had had catatonic symptoms at least once, we found 66 family members who had suffered from schizophrenia (12.2%). This is quite different from the morbidity risks reported in recent family studies on "schizophrenia as a whole" [Kendler and Diehl, 1993]. In the 2 recent studies, there were 41 cases of schizophrenia in 739 people at risk, i.e., the morbidity risk for schizophrenia was 5.6% [Kendler et al., 1993; Maier et al., 1993]. However, taking into account the heterogeneity of the disease, our results confirm studies made by Kallmann [1938] and Scharfetter and Nüsperli [1980] that demonstrated increased familial loading in catatonic schizophrenics as compared to other clinical subforms.

Morbidity Risk in Relatives of Systematic Catatonics

First-degree relatives of systematically catatonic patients have only a low risk of developing the disease. There is no familial aggregation of psychoses. The morbidity risk was at a level of 4.6% among first-degree relatives. Using life-table analysis, mothers had a lifetime morbidity risk of 6.8%, fathers 2.0%, and sibs 3.0%. This corroborates Leonhard's report [1986] (2.7–3.5% according to Weinberg's abridged method). In most cases, therefore, systematic catatonia seems to represent sporadic forms of schizophrenic psychoses. A previous study linked systematic schizophrenia to a surplus of maternal infectious diseases during midgestation, followed by an increased rate of obstetric complications [Stöber et al., 1992, 1993, 1994]. There is evidence that a disturbance in brain maturation in the second trimester is involved in the etiology of schizophrenia [Jakob and Beckmann, 1986; Mednick et al., 1988], and it is hypothesized that there may be a link between exogenously induced disturbances of prenatal brain maturation and the development of chronic systematic schizophrenia in adulthood [Stöber et al., 1992; Beckmann and Franzek, 1992].

Familial Aggregation of Homogenous Psychoses in Periodic Catatonia

The results of the present study suggest that increased familial incidence in catatonic psychoses reported in some earlier studies is confined to the clinical subtype of periodic catatonia [Slater and Cowie, 1971; Scharfetter and Nüsperli, 1980]. In our study, 59% of the families were multiple afflicted. In 49 multiple-afflicted nuclear families with periodic catatonia, there were 59 homogenous types of catatonic schizophrenias among 323 first-degree relatives. Using life-table analysis, the corrected morbidity risk for all first-degree relatives was 26.9%. There was a life-time morbidity risk of 33.7% for mothers, 15.4% for fathers, and 24.4% for sibs.

The probability of affliction with periodic catatonia was not influenced by gender as an assumed prognostic variable. For all groups of first-degree relatives the morbidity risk of periodic catatonia is significantly greater than that of systematic catatonia (Table III). Homogeneity of familial psychoses has been a given fact for experienced clinicians and psychiatrists since Kraepelin, Bleuler, Kallmann, and Rüdin. However, reducing clinical psychopathology to schedules of negative function and factor analysis of positive and negative symptoms, Kendler et al. [1994] found no relationship between patterns of familial psychopathology in "schizophrenia." In periodic catatonia there was a high degree of homogeneity of symptoms and disease course among first and second-degree relatives [Stöber et al., 1995]. A blind diagnostic review of hospital records of 63 psychiatrically hospitalized relatives of periodically catatonic patients resulted in 59 diagnoses of chronic schizophrenia. The interrater agreement was kappa 0.93. Seventy-six percent of all living first-degree relatives with previous hospitalization could be examined and all of them had psychopathological symptoms characteristic of periodic catatonia. We found no heterogeneity in catatonic psychoses among these families [Stöber et al., 1995] nor any tendency among the first-

TABLE III. Morbidity Risk in First-Degree Relatives of Patients With Periodic and Systematic Catatonia (Life-Table Analysis Using Kaplan-Meier Estimates)

	Morbidity risk (%)		
	Mothers	Fathers	Sibs
Systematic catatonia	6.8	2.0	3.0
Periodic catatonia	33.7	15.4	24.6
Level of significance	$P < 0.005$	$P < 0.02$	$P < 0.01$

degree relatives of periodically catatonic patients to suffer from major depressive disorders. Studies reporting a familial relationship between catatonia and affective pictures frequently used a rather broad diagnostic concept of catatonia [Scharfetter and Nüsperli, 1980; Kendler et al., 1988]. Of the 63 first-degree relatives, 24% were deceased. The chart reviews revealed in all of them a diagnosis of DSM-III-R schizophrenia with catatonic features. Because there were no personal examinations, however, further subclassification was impossible.

Preponderance of Mothers in Schizophrenic Parents

It is known that among parents of schizophrenics, afflicted mothers predominate over fathers by approximately 2:1 [Slater and Cowie, 1971; Bleuler, 1978]. This was sometimes regarded as supporting the psychogenic theory of schizophrenia [Zerbin-Rüdin, 1967]. Now it is agreed that the surplus of schizophrenic mothers results from a combination of an earlier onset of the disease in men (reducing their eligibility for marriage or reproducing) and earlier marriages in women, i.e., psychosis in women often appears after reproduction [Essen-Møller, 1963; Slater and Cowie, 1971; Gottesman and Shields, 1982]. Our life-table analysis (Fig. 4) confirms that there are actually no differences in morbidity curves between mothers and fathers. Up to the age of 50 the risk is approximately 15% for both parents. From then on the morbidity risk of mothers rises continuously up to a level of 33.7% while that of fathers remains constant. Thus, the difference in morbidity risk may be attributable to the lower incidence among fathers late in life resulting from men's shorter life expectancy.

Morbidity Risk for Parents and Sibs of Periodically Catatonic Patients

Concurring with earlier literature [Gottesman and Shields, 1982], recent family studies recorded only a small quota (1.1–1.3%) of parents with schizophrenia. This may be due either to schizophrenics' reduced fertility rate or to the fact that only parents were selected as probands [Kendler et al., 1993] and being a parent would be a kind of screening procedure against having schizophrenia [Risch, 1983]. On the contrary, we found more afflicted parents than sibs in periodic catatonia; sporadically systematically catatonic patients had the same mean number of sibs as patients suffering from familial periodic catatonia. In 29 (35%) families with periodically catatonic probands unequivocally unilineal transmission was evident (20 maternal and 9 paternal derivations). In only 2 families were both parents afflicted (2%). In our sampling, the number of schizophrenic parents of probands (33 of 161 parents) was higher than the number of schizophrenic sibs (26 of 162 sibs). In pairwise comparisons of patients and their parents there were patterns of anticipation, i.e., the probands' age at onset was significantly lower than that of their parents. Anticipation still occurred in pedigrees with 3 successive generations and was also evident in parents with an early onset of the disease, indicating that anticipation did exist [Stöber et al., 1995]. In 8 of the 83 families we found 3-generation pedigrees with periodic catatonia (Fig. 5). Given that psychiatric care was not institutionalized until this century, this figure may well be too low.

A high quota of 3-generation pedigrees with homogenous periodic catatonia (59% of multiple-afflicted families) unilineal transmission, a morbidity risk of 26.4% in first-degree relatives, a definitive surplus of afflicted parents as compared to afflicted sibs, and anticipation emphasize the fact that periodic catatonia is a distinct type of chronic schizophrenia with a major gene effect [Vogel and Motulsky, 1986; McGriffith et al., 1992]. The gap of 50% in the expected morbidity rate might result from late manifestations and the fact that not every afflicted family member required hospital treatment. It was recommended that only those hospitalized for definite schizophrenia be allocated to the group of afflicted family members. From personal examinations, Leonhard found that nearly 50% of the parents were psychotic or abnormal indicating a dominant mode of autosomal inheritance [von Trostorff, 1981].

Implications

In a clinical approach we investigated the degree of familial aggregation in chronic DSM-III-R schizophrenia, involving catatonic symptoms at least once in the course of the disease. It was evident that the clinical subclassification of the sample into periodically and systematically catatonic patients using the Leonhard classification was reliable and valid. The study contradicts the unitary or continuum model of mental illness [Baron et al., 1985; Crow, 1986; Maier et al., 1993]. Periodic and systematic catatonia proved to be well-defined clinical entities. Statistically, they showed significantly different genetic backgrounds. Systematic catatonia seems to appear sporadically in most cases. In contrast, periodic catatonia has a high morbidity risk in familial aggregation. Psychosis homogeneity and unilineal vertical transmission with anticipation were consistent with a major gene effect. Our findings shed new light on the current discussion of etiological factors [Murray et al., 1992; Kendler and Diehl, 1993]. A well-defined subgroup of DSM-III-R schizophrenia indicates a major gene effect and seems to be a promising candidate for molecular genetic evaluation.

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